

Claims:

1. A process for the production of a composite material comprising collagen, brushite and one or more glycosaminoglycans, said process comprising the steps of providing an acidic aqueous solution comprising collagen, a calcium source and a phosphorous source and one or more glycosaminoglycans, and precipitating the collagen, the brushite and the one or more glycosaminoglycans together from the aqueous solution to form a triple co-precipitate.
2. A process as claimed in claim 1, wherein the solution has a pH of from 2.5 to 6.5, more preferably from 2.5 to 5.5.
3. A process as claimed in claim 2, wherein the solution has a pH of from 3 to 4.5.
4. A process as claimed in claim 3, wherein the solution has a pH of from 3.8 to 4.2.
5. A process as claimed in any one of the preceding claims, wherein the calcium source is selected from one or more of calcium nitrate, calcium acetate, calcium chloride, calcium carbonate and calcium alkoxide, calcium hydroxide, calcium silicate, calcium sulphate, calcium gluconate and the calcium salt of heparin.
6. A process as claimed in any one of the preceding claims, wherein the phosphorus source is selected from one or more of ammonium-dihydrogen phosphate, diammonium

hydrogen phosphate, phosphoric acid, disodium hydrogen orthophosphate 2-hydrate and trimethyl phosphate.

7. A process as claimed in any one of the preceding
5 claims, wherein the one or more glycosaminoglycans are selected from chondroitin sulphate, dermatin sulphate, heparin, heparin sulphate, keratin sulphate and hyaluronic acid.

10 8. A process as claimed in any one of the preceding claims, wherein the solution has a temperature of from 4 to 50°C.

9. A process as claimed in any one of the preceding
15 claims, wherein the solution has a temperature of from 15 to 40°C.

10. A process as claimed in any one of the preceding claims wherein the ratio of collagen to the total amount of one or
20 more glycosaminoglycans in the solution is from 8:1 to 30:1 by weight.

11. A process as claimed in any one of the preceding claims, wherein the solution comprises calcium ions and the
25 ratio of collagen to the calcium ions is from 1:40 to 500:1 by weight, preferably from 1:40 to 250:1 by weight, more preferably from 1:13 to 5:4.

12. A process as claimed in any one of the preceding
30 claims, wherein ratio of collagen to brushite in the co-precipitate is from 10:1 to 1:100 by weight, preferably from 5:1 to 1:20.

13. A process as claimed in any one of the preceding claims
wherein the solution comprises calcium ions and the
concentration of calcium ions in solution is from 0.00025 to
5 1 M, preferably from 0.001 to 1 M.

14. A process as claimed in any one of the preceding claims
wherein the solution comprises phosphate ions and the
concentration of phosphate ions in solution is from 0.00025 to 1 M,
10 preferably from 0.001 to 1 M.

15. A process as claimed in any one of the preceding claims
wherein the concentration of collagen in the solution is
from 1.0 to 20 g/L, more preferably 1.0 to 10 g/L.

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16. A process as claimed in any one of the preceding claims
wherein the total concentration of the one or more
glycosaminoglycans in the solution is from 0.01 to 1.5 g/L,
more preferably from 0.01 to 1 g/L.

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17. A process for the production of a composite biomaterial
comprising collagen, octacalcium phosphate and one or more
glycosaminoglycans, said process comprising the steps of
providing a composite material comprising collagen,
25 brushite and one or more glycosaminoglycans, and
converting at least some of the brushite in the
composite material to octacalcium phosphate by
hydrolysis.

30 18. A process as claimed in claim 17, wherein the composite
material comprises or consists essentially of a triple co-

precipitate comprising collagen, brushite and one or more glycosaminoglycans.

19. A process as claimed in claim 18, wherein the triple
5 co-precipitate is formed according to a process as defined
in any one of claims 1 to 16.

20. A process as claimed in any one of claims 17 to 19,
wherein the step of hydrolysis of brushite to octacalcium
10 phosphate comprises contacting the composite material with
an aqueous solution, said aqueous solution being at or above
the pH at which octacalcium phosphate becomes
thermodynamically more stable than brushite.

15 21. A process as claimed in claim 20, wherein said aqueous
solution has a pH of from 6 to 8.

22. A process as claimed in claim 21, wherein said aqueous
solution has a pH of from 6.3 to 7.

20 23. A process as claimed in claim 22, wherein said aqueous
solution has pH of about 6.65.

24. A process for the production of a composite biomaterial
25 comprising collagen, apatite and one or more
glycosaminoglycans, said process comprising the steps of
providing a composite material comprising collagen,
brushite and one or more glycosaminoglycans, and
converting at least some of the brushite in the
30 composite material to apatite by hydrolysis.

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25. A process as claimed in claim 24, wherein the composite material comprises or consists essentially of a triple co-precipitate comprising collagen, brushite and one or more glycosaminoglycans.

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26. A process as claimed in claim 25, wherein the triple co-precipitate is formed according to a process as defined in any one of claims 1 to 16.

10 27. A process as claimed in any one of claims 24 to 26, wherein the step of hydrolysis of brushite to apatite comprises contacting the composite material with an aqueous solution, said aqueous solution being at or above the pH at which apatite becomes thermodynamically more stable than
15 brushite.

28. A process as claimed in claim 27, wherein said aqueous solution has a pH of from 6.65 to 9, preferably from 7 to 8.5.

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29. A process as claimed in any one of claims 17 to 28, wherein the conversion of brushite to octacalcium phosphate and/or apatite is carried out at a temperature of from 20 to 50°C, preferably from 30 to 40°C.

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30. A process as claimed in claim 29, wherein said temperature is from 36 to 38°C.

30 31. A process as claimed in claim 30, wherein said temperature is about 37°C.

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32. A process as claimed in any one of the preceding claims further comprising the steps of crosslinking the collagen and the one or more glycosaminoglycans in the composite material or triple co-precipitate.

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33. A process as claimed in claim 32, wherein, if at least some of the brushite is converted to octacalcium phosphate and/or apatite, the glycosaminoglycan is crosslinked prior to the conversion of the brushite to octacalcium phosphate 10 and/or apatite.

34. A process as claimed in claim 33, wherein the crosslinking is effected by one or more of subjecting the triple co-precipitate to gamma radiation and/or ultraviolet 15 radiation, non-enzymatic glycation with a simple sugar such as glucose, mannose, ribose or sucrose, contacting the triple co-precipitate with glutaraldehyde, ethyl dimethylaminopropyl carbodiimide and/or nor-dihydoguariaretic acid, and subjecting the triple co- 20 precipitate to a dehydrothermal treatment.

35. A process as claimed in any one of claims 32 to 34, wherein, if at least some of the brushite is converted to octacalcium phosphate and/or apatite, the collagen and one 25 or more of glycosaminoglycans are crosslinked subsequent to the conversion of the brushite to octacalcium phosphate and/or apatite.

36. A process as claimed in claim 35, wherein the crosslinking is effected by one or more of: subjecting the triple co-precipitate to gamma radiation, ultraviolet 30 radiation or dehydrothermic treatment, non-enzymatic

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glycation with a simple sugar such as glucose, mannose, ribose and sucrose, contacting the triple co-precipitate with one or more of glutaraldehyde ethyl dimethylaminopropyl carbodiimide and/or nor-dihydoguariaretic acid.

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37. A process as claimed in any one of claims 32 to 36, wherein the collagen and the one or more glycosaminoglycan are crosslinked both prior to and subsequent to conversion of the brushite to octacalcium phosphate and/or apatite.

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38. A process as claimed in any one of the preceding claims, further comprising the step of shaping the composite biomaterial into a structure suitable for use as a bone or dental substitute.

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39. A process as claimed in any claim 38, wherein the composite material is shaped using a technique selected from filtration and low temperature drying, freeze drying, injection moulding and cold pressing.

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40. A precursor material for transforming into a synthetic biomaterial, said precursor material comprising a composite material comprising collagen, brushite and one or more glycosaminoglycans.

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41. A precursor material as claimed in claim 40, wherein the composite material comprises or consists essentially of a triple co-precipitate comprising collagen, brushite and one or more glycosaminoglycans.

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42. A precursor material as claimed in claim 41, wherein said triple co-precipitate is produced according to a process as defined in any one of claims 1 to 16.

5 43. A composite biomaterial comprising collagen, brushite and one or more glycosaminoglycans, which biomaterial is obtainable by a process as defined in any one of claims 1 to 39.

10 44. A composite biomaterial comprising collagen, octacalcium phosphate and one or more glycosaminoglycans, which biomaterial is obtainable by a process as defined in any one of claims 17 to 39.

15 45. A composite biomaterial comprising collagen, apatite and one or more glycosaminoglycans, which biomaterial is obtainable by a process as defined in any one of claims 24 to 39.

20 46. A composite biomaterial comprising collagen, brushite and one or more glycosaminoglycans.

47. A composite biomaterial comprising collagen, octacalcium phosphate and one or more glycosaminoglycans.

25 48. A composite biomaterial as claimed in any one of claims 43 to 47 for use as a substitute bone or dental material.

30 49. A composite biomaterial comprising a triple co-precipitate of collagen, brushite and one or more glycosaminoglycans.

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50. A material as claimed in any one of claims 40 to 49, wherein the collagen and the one or more glycosaminoglycans have been crosslinked.

5 51. A material as claimed in any one of claims 40 to 50, wherein the collagen is present in the material in an amount of from 5 to 90 wt%, preferably from 15 to 60 wt%.

10 52. A material as claimed in any one of claims 40 to 51, wherein the one or more glycosaminoglycans are present in the material in an amount of from 0.01 to 12 wt%, preferably from 1 to 5.5 wt%.

15 53. A material as claimed in any one of claims 40 to 52, wherein, if the material comprises brushite, the ratio of collagen to brushite is 10:1 to 1:100 by weight, preferably from 5:1 to 1:20 by weight.

20 54. A material as claimed in any one of claims 40 to 52, wherein, if the material comprises octacalcium phosphate, the ratio of collagen to octacalcium phosphate is 10:1 to 1:100 by weight, preferably from 5:1 to 1:20 by weight.

25 55. A material as claimed in any one of claims 40 to 54, wherein the ratio of collagen to the total amount of one or more glycosaminoglycans is from 8:1 to 30:1 by weight.

30 56. A biomaterial comprising particles of one or more calcium phosphate materials, collagen and one or more glycosaminoglycans, wherein said collagen and said one or more glycosaminoglycans are crosslinked and form a matrix,

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 said particles of calcium phosphate material are dispersed in said matrix, and

 said calcium phosphate material is selected from one or more of brushite, octacalcium phosphate and/or apatite.

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57. A synthetic bone material, bone implant, bone graft, bone substitute, bone scaffold, filler, coating or cement comprising a material as defined in any one of claims 43 to 56.

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